UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/616,371	03/15/1996	JONATHAN S. STAMLER	DUK96-03PA	3375

21005 7590 12/23/2003

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/616,371	STAMLER, JONATHAN S.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,16-30,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,16-30,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/01;4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

Applicant's provision of appendix claims (e.g. mailed 7/28/03) is acknowledged with appreciation.

Any prior indication of allowable subject matter is hereby withdrawn in view of the following new office action..

Status of the Claims

Claims 4, 16-30 and 33-34 are currently pending and under consideration. .

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim Rejections - 35 USC § 102/103

4. Claims 16-21 and 26-30 are rejected under 35 U.S.C. 102(e) as being anticipated by, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,583,113 (6/03: filed 3/95 or earlier).

Stamler et al teaches (claims and discloses)compositions comprising nitrosylated heme proteins (including (S) nitrosated/nitrosylate hemoglobin), their intermediate low mw nitrosothiols (e.g. see col. 1) and the use thereof to deliver NO/O2 to tissues for the prevention/treatment of various diseases/disorders including cardiovascular/respiratory diseases/disorders (e.g. ARDS, heart disease etc.) . See e.g. col .1-2 ; col. 4; col. 5; col. 9-12; examples; patent claims. The reference teaching of utilizing NO donating compounds to deliver NO/O2 to tissues (e.g. for therapeutic purposes) would anticipate or alternatively render obvious the use of blood substitutes which would additionally incorporate NO donating hemoglobin compounds to deliver oxygen. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The reference teaching of delivering S-nitrosylated Hb to the same

host in the same way would inherently result in "scavenging oxygen radicals" E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The reference teaching of vasodilation (e.g. see examples) would anticipate or render obvious the use of NO donors, such as S-nitrosated Hb and low mw S-nitrosothiols for treating hypertension.

5. Claims 18-21 and 26-30 are rejected under 35 U.S.C. 102(e) as being anticipated, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier).

Stamler et al. teach compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of

hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties and thus would potentiate NO (and oxygen) delivery. The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

6. Claims 4, 16-19, 21-27 and 29-30 are rejected under 35 U.S.C. 102(e) as being anticipated, or in the alternative obvious over Stamler et al., US Pat. No. 6,153,186 (11/00: effectively filed 9/95 by 60/003,801).

Stamler et al. '186 teach the delivery of NO to a mammal by administering low moleculer weight S-nitrosothiols and/or S-nitrosated hemoglobin to treat"medical conditions characterized by abnormal oxygen metabolism ... abnormal O2 delivery" (e.g. see col. 2) which includes hypertension, sickle cell anemia, organ preservation, stroke. E.g. see abstract; col. 5 col. 9, examples and patent claims. The reference anticipates or in the alternative renders obvious direct as well as indirect (through cell delivery) administration of S-nitrosothiols. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

Claim Rejections - 35 USC § 103

7. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al, WO 93/09806 (5/93) or its U.S. equivalent US Pat. 6,291,424 (9/01: filed 3/95 or earlier).

US Pat. No. 6,291,424 (claiming S-nitrosated hemoglobins) and WO 93/09806 appear to contain identical disclosures and are equally applicable in the present rejection. However, for the purposes of brevity, the present rejection will be discuss the WO 93 document.

The presently claimed invention is directed to producing a composition comprising either SNO-Hb[FeII]O2 (produced in the presence of oxygen) or SNO-Hb[FeII] (produced in the absence of oxygen) by reacting "excess nitrosating agent"

(e.g. low molecular weight nitrosothiols i.e. S-nitroglutathione et.al.) with purified hemoglobin (e.g. claims 10-11 and 13-14). Claims 12 and 15 specifically select a low molecular weight S-nitrosothiol as the nitrosating agent.

Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

However, the above two reference methods for thiol nitrosylation fail to disclose the use of "excess" nitrosating agent, and preferably the selection of a low molecular weight S-nitrosothiol as the nitrosating agent for thionitrosylation of hemoglobin.

But the Stamler reference (e.g. Example 19 on pages 58-59) specifically discloses the preferential selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) instead of acidic Na NO2 as utilized for tPA due to reduced ability of the SNOAC as compared with acidic nitrate to bind at the redox metal which reduces oxygen binding affinity.

Further, the use of "excess nitrosating agent" in either reaction 1. or 2 above is suggested by the Stamler reference since providing a greater concentration of NO serves to enhance the therapeutic efficacy of the nitrosylated proteins (e.g. see bottom of page 23-top of 24)

It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH7.4 in the the making and storage of vaious thiol proteins. Additionally, the thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26).
Optimization of reaction conditions, including pH, is within the skill of the art.

Additionally, it is a matter of obvious design choice to select anaerobic conditions for making a deoxygenated hemoglobin derivative and aerobic conditions when desiring to make an oxygenated hemoglobin derivative.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to synthesize thionitrosylated hemoglobin by using "excess" nitrosating agent, and preferably a low molecular weight S-nitrosothiol, and to further optimize pH during nitrosylation to utilize physiological conditions to form a more stable nitrosylated oxy/deoxy hemoglobin.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In*

re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 16-21, 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 (especially claims 7-9 and 17) of copending Application No. 10/216,865 (PG PUB US 2003/0079674A1 Jan 9, 2003). Although the conflicting claims are not identical, they are not patentably distinct from each other because the application claims compositions comprising S- nitroso hemoglobins and uses thereof which comprise NO delivery, including treating/preventing cardiovascular/respiratory disorders (e.g. Heart disease, ARDS etc: see patent claim 9 interpreted in light of disclosure: e.g. at page 6) . Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins. The adminsitration of hemoglobins to patients for the treatment of cv/pulmonary disorders would inherently result in the scavenging of oxygen free radicals and/or the reduction of blood pressure (e.g. vasodilatory effect).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 16-21, 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,583,113 (6/03). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims teach compositions comprising nitrosated/nitrosylated heme proteins (e.g.including S-nitrosylated hemoglobins : see cliams 1-3) and their use (E.g. delivery of NO to tissues via administration) in treaing/preveinting diseases including cardiovascular diseases such as ARDS (E.g. see claims 1 and 4:col. 11-12) and heart disease. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

11. Claims 16-21, 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-65 of Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier) as interpreted in light of the specification regarding the scope of treatment of vasculature damage and inherency.

Stamler et al. teach (e.g. disclose and claim) compositions that comprise nitric oxide (NO adducts) (e.g upon administration), including S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature

which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Additionally, the reference teaches combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to "potentiation of NO delivery". The reference teaching of compositions comprising nitrosated/nitrosylated hemoglobins and/or low MW S-nitrosothiols for administration would inherently, upon administration, produce the scavenging of oxygen free radicals as reduced blood pressure (E.g. vasodilatory effect).. E.g. The prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Further, the reference discloses the treatment of damaged blood vessels as well as the prevention/treating of cardivasular/respiratory diseases (e.g. heart disease and ARDS) . See claims and col. 1-4; patent claims. Deoxy- hemoglobins are within the scope of the disclosed/patented invention (as immediately envisaged) or alternatively represents an obvious variant thereof of oxy-hemoglobins.

12. Claims 4, 16-19, 21-27 and 29-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of

Stamler et al. US Pat. No. 6,153,186 (11/00: effectively filed 9/95 by 60/003,801). as interpreted in light of the patent specification regarding the scope of treatment of a mamamal in need thereof (e.g. patent claims 8-9) and inherency

The patent claims of Stamler et al. '186 teach the delivery of NO/O2 to a mammal by administering low moleculer weight S-nitrosothiols and/or S-nitrosated hemoglobin via a blood substitute comprising these compounds in order to deliver NO to tissues to treat a "mammal in need thereof". The patent specification describes treating mammal in need thereof to encompass "medical conditions characterized by abnormal oxygen metabolism ... abnormal O2 delivery" (e.g. see col. 2) which includes hypertension, sickle cell anemia, organ preservation, stroke. E.g. see abstract; col. 5 col. 9, examples and patent claims. The reference anticipates or in the alternative renders obvious direct as well as indirect (through cell delivery) administration of S-nitrosothiols. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

13. Claims 16-21, 26-30 of this application conflict with claims which are present in Application No.08/667,003 and 08/796,164.

37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 703-305-7556. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 703-306-3217. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bennett Celsa
Primary Examiner
Art Unit 1639

BC